Personalized cancer therapies based on spatial heterogeneity of the tumor ecosystem

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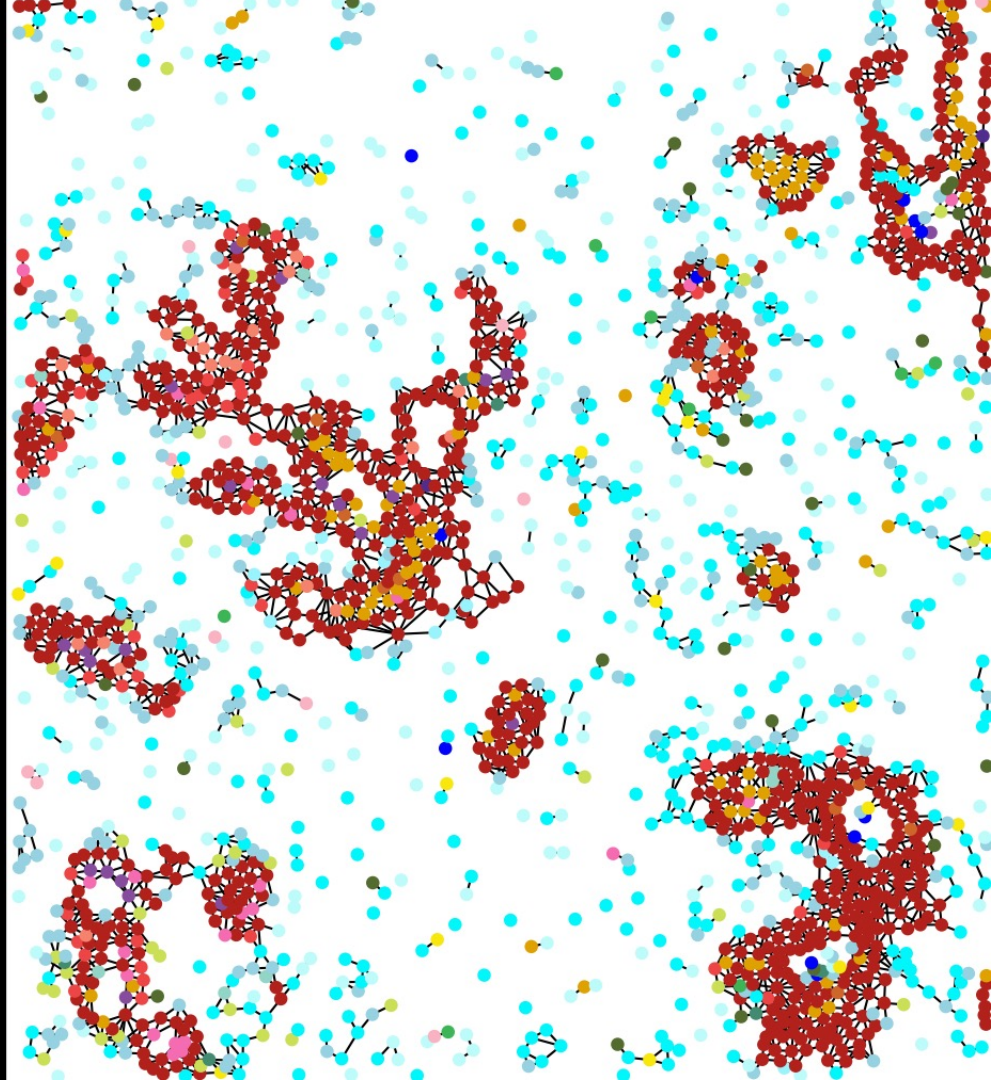
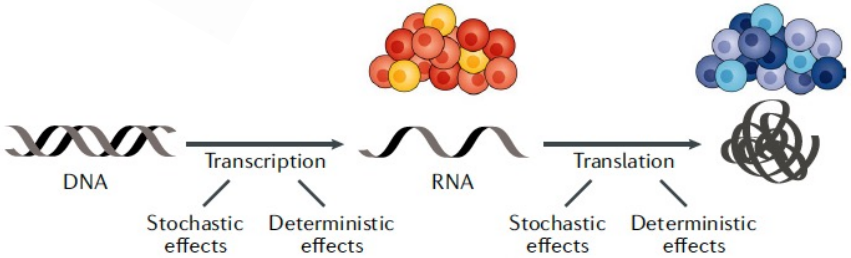
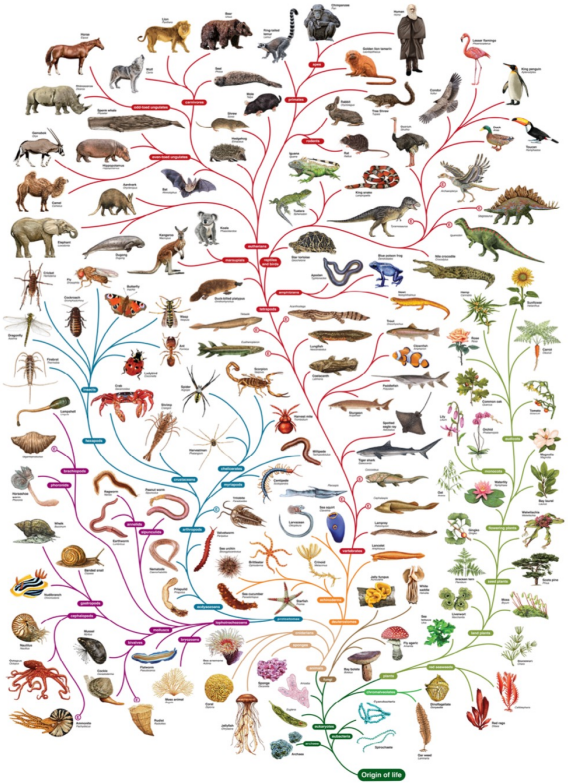


Stochasticity in biological systems

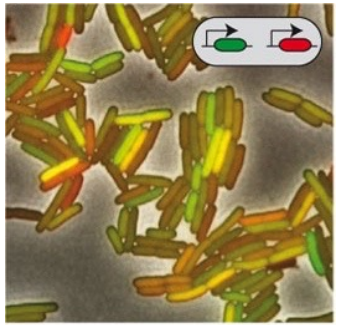


Eling, *et al. Nat. Rev. Genet* (2019)

Evolution

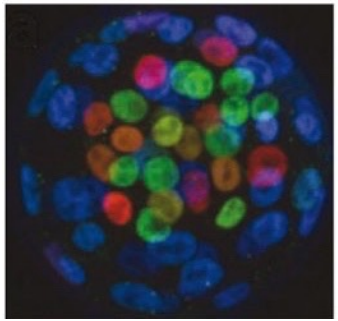


Gene expression



Elowitz, *et al. Science* (2002)

Differentiation



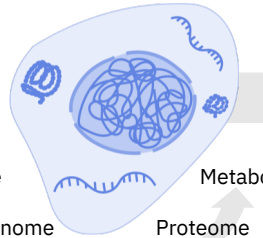
Eldar, *et al. Nature* (2010)

Pattern formation

Image credit: https://ifisc.uib-csic.es/

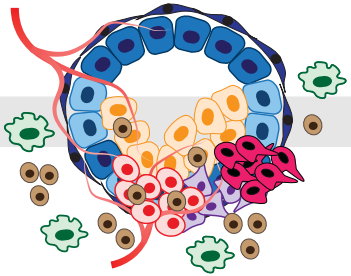
Tumor heterogeneity across scales

Intra-cell



Intrinsic

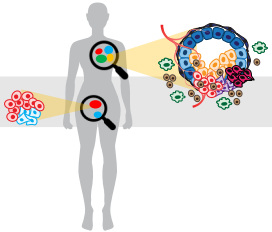
Intra-tumor



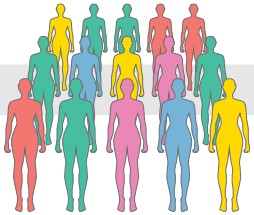
Tumor microenvironment

Extrinsic

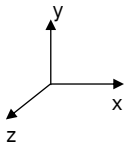
Intra-patient



Inter-patient

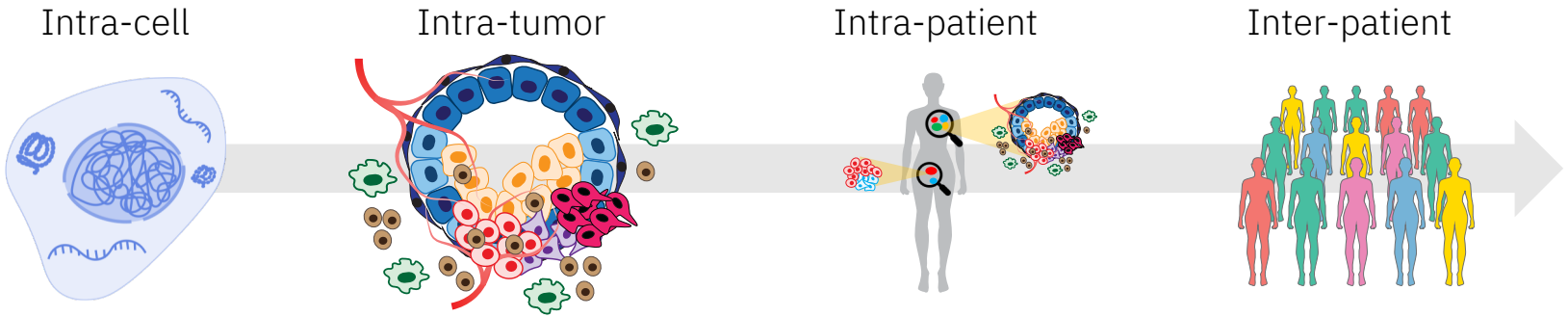


Spatial



Temporal

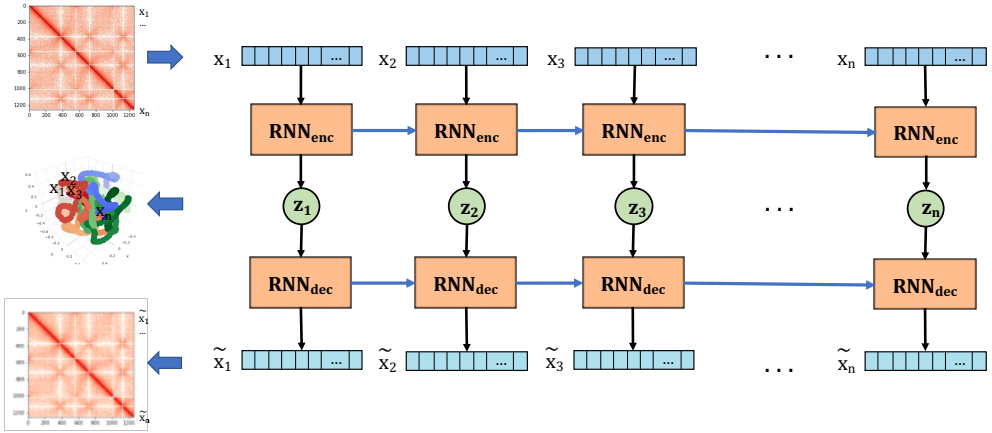
Tumor heterogeneity across scales



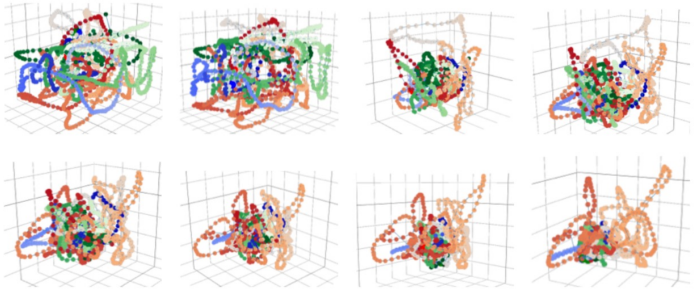
Heterogeneity in chromatin folding

Cristina Cristescu

REACH-3D: inference of 3D chromatin structure from Hi-C data



Temporal heterogeneity across the cell cycle



Prediction of 3D chromatin structure of the full fission yeast genome across different timepoints of its cell cycle

Papers:

Cristescu *et al*, (2018) Inference of 3D chromatin structure and its temporal behavior, NeurIPS MLMM Workshop

Meynier and Rapsomaniki (2021). Modeling the 3D Chromatin Structure from Hi-C Data with Transfer Learning. LMRL NeurIPS workshop

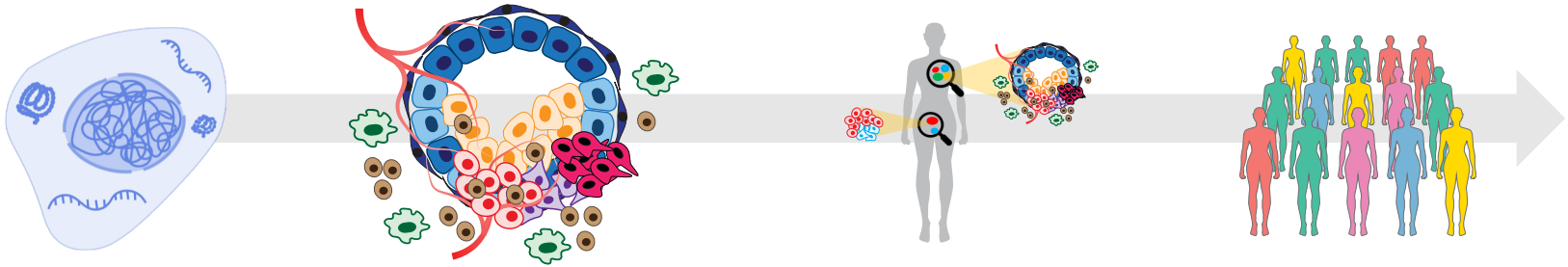
Tumor heterogeneity across scales

Intra-cell

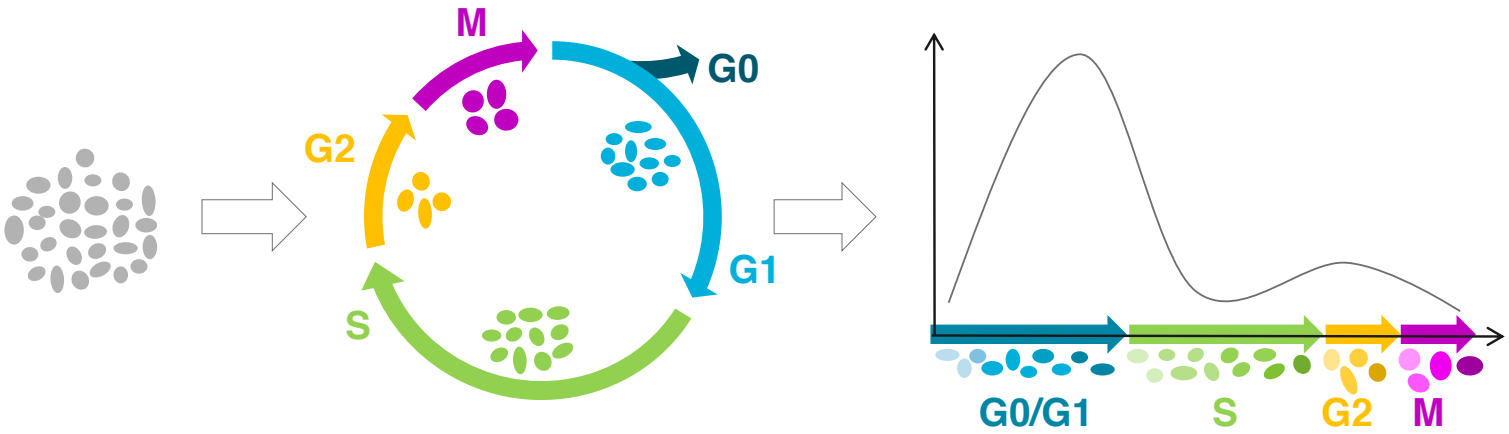
Intra-tumor

Intra-patient

Inter-patient

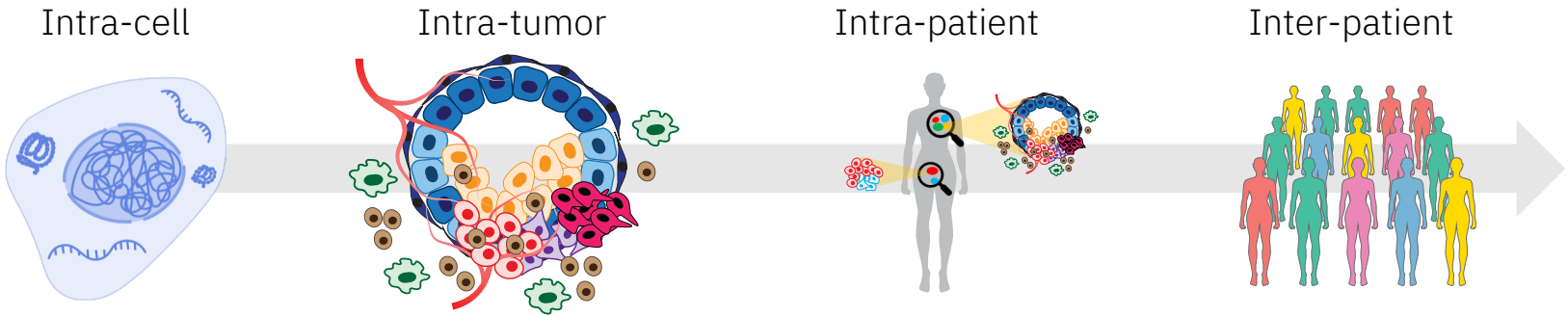


CellCycle**TRACER** | Trajectories of cell cycle evolution

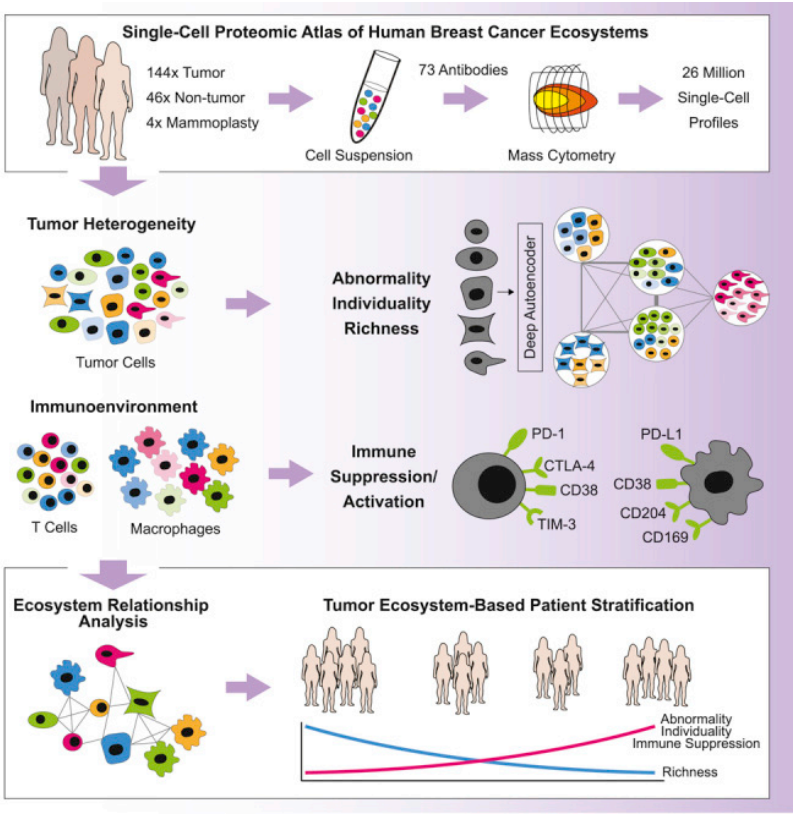


Paper: Rapsomaniki *et al*. (2018). *Nature Communications*
Software: https://www.zurich.ibm.com/cellcycletracer/

Tumor heterogeneity across scales



A Single-Cell Atlas of Breast Cancer Ecosystems

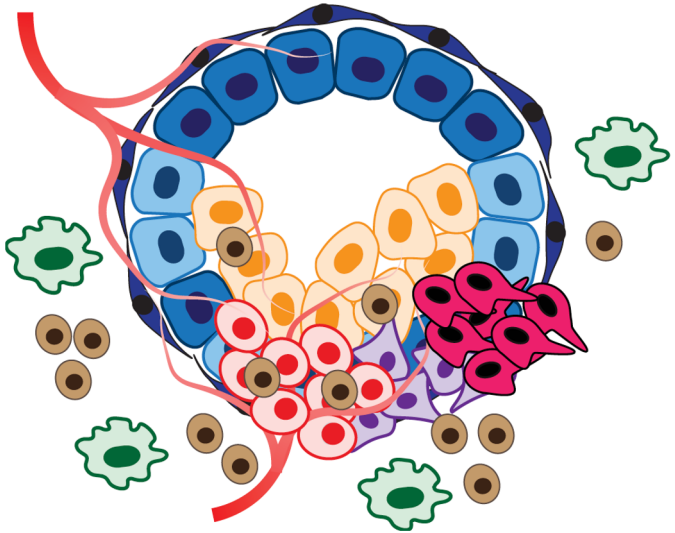


Richness	Abnormality	Individuality
How many cell types exist in the tumor ecosystem?	How much have the tumor cells deviated from non-tumor?	How distinct is the tumor within the cohort?

- Ecosystem-based approach enables **patient stratification**
- Aggressive tumors are **low in richness** and **high in abnormality and individuality**: few, highly abnormal cell subtypes

Paper: Wagner *et al.*, (2019), *Cell* https://github.com/AI4SCR/scQUEST

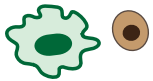
Tumors are **spatially** heterogeneous ecosystems



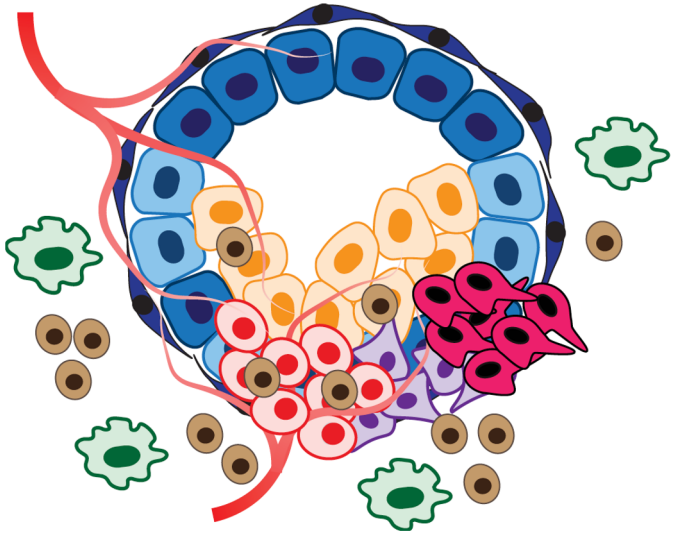
Normal cells

Tumor cells

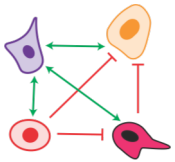
Immune cells



Tumors are **spatially** heterogeneous ecosystems



Tumor-tumor interactions:



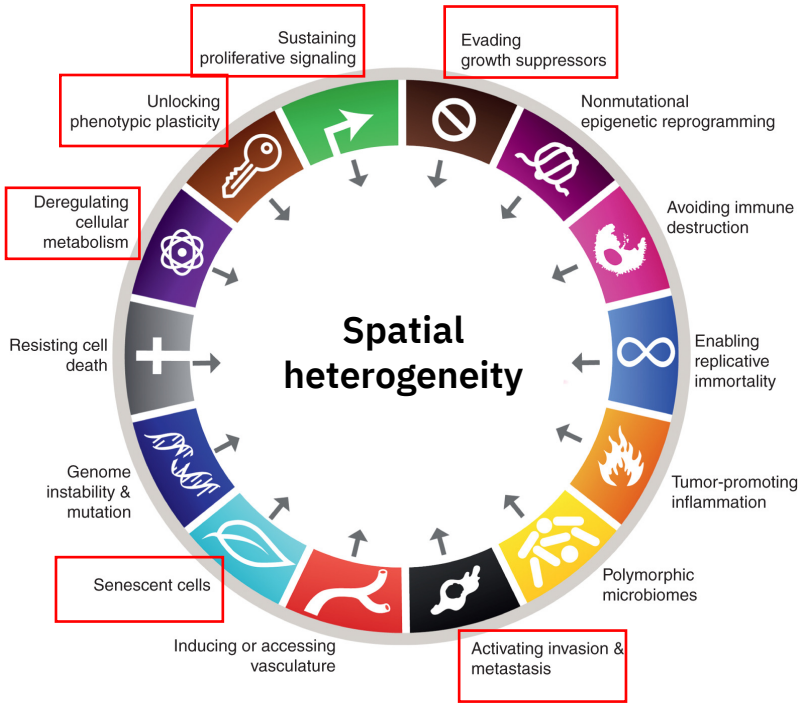
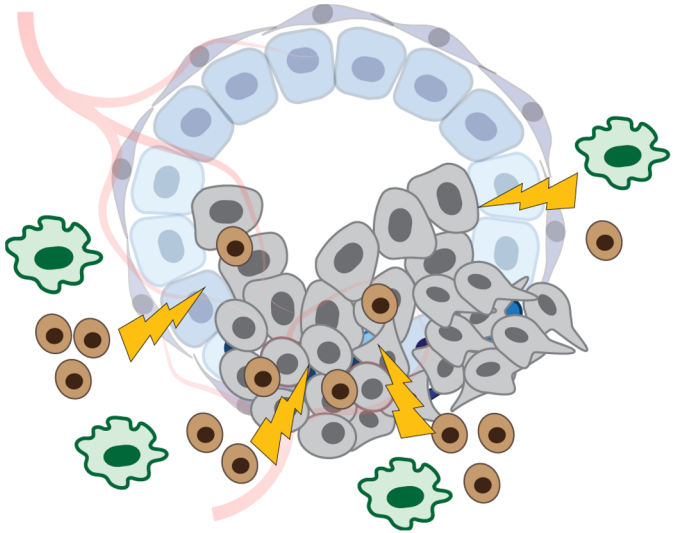


Image from: Hanahan et al., 2022

Tumors are **spatially** heterogeneous ecosystems



Immune attack:

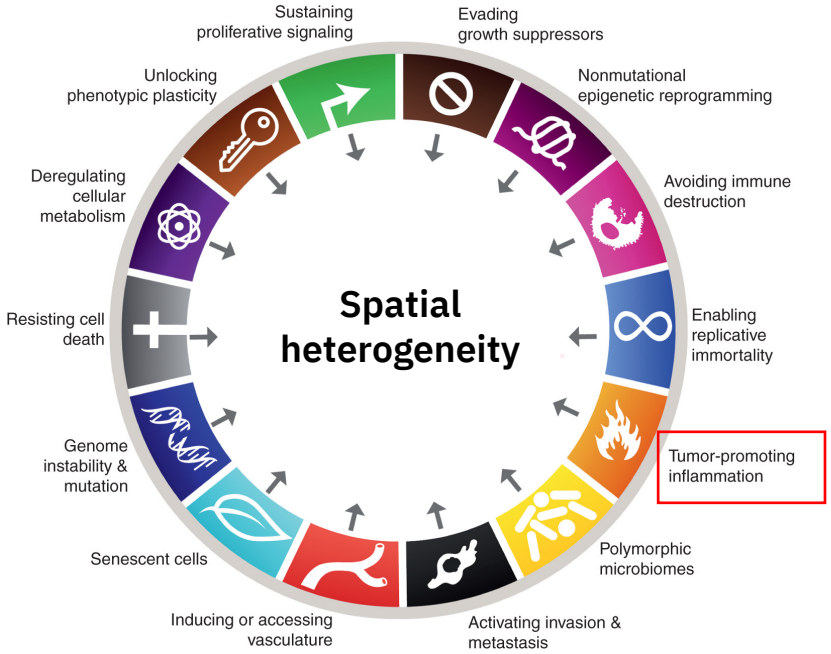
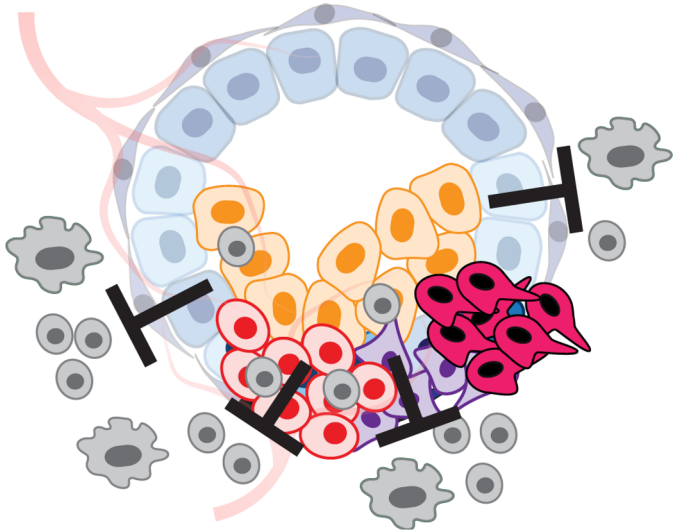


Image from: Hanahan et al., 2022

Tumors are **spatially** heterogeneous ecosystems



Immune suppresion:

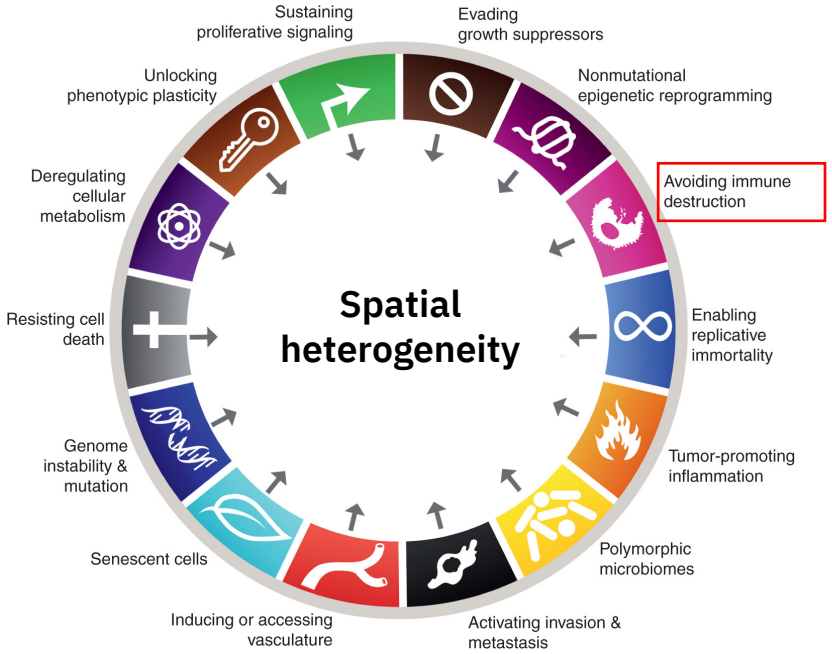
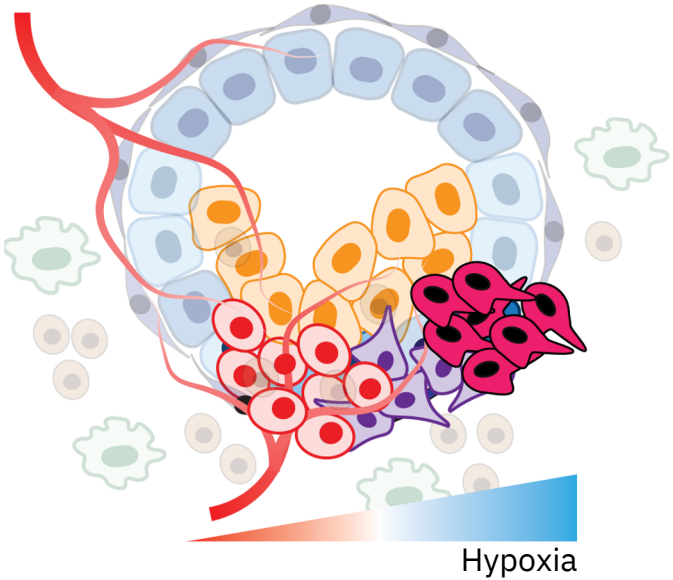


Image from: Hanahan et al., 2022

Tumors are **spatially** heterogeneous ecosystems



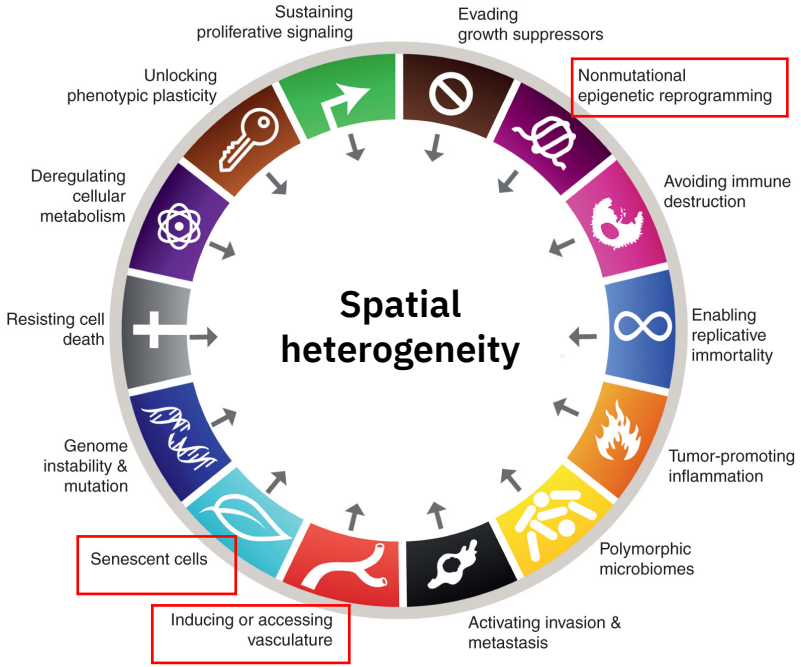
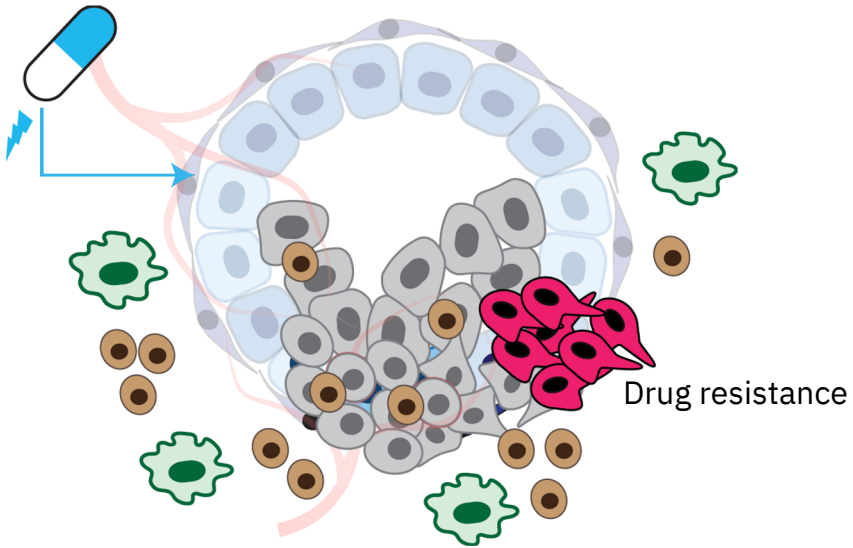


Image from: Hanahan et al., 2022

Tumors are **spatially** heterogeneous ecosystems



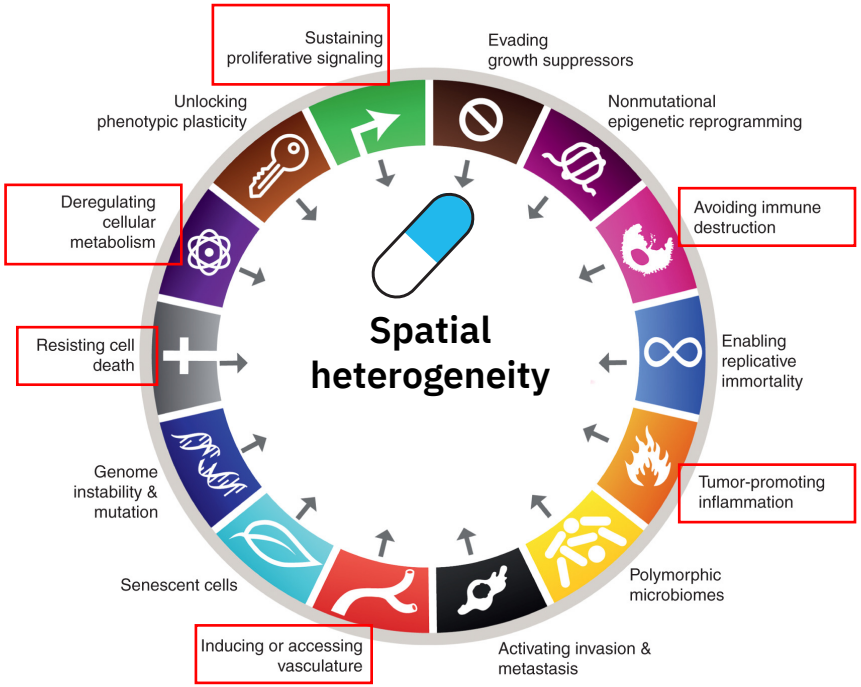
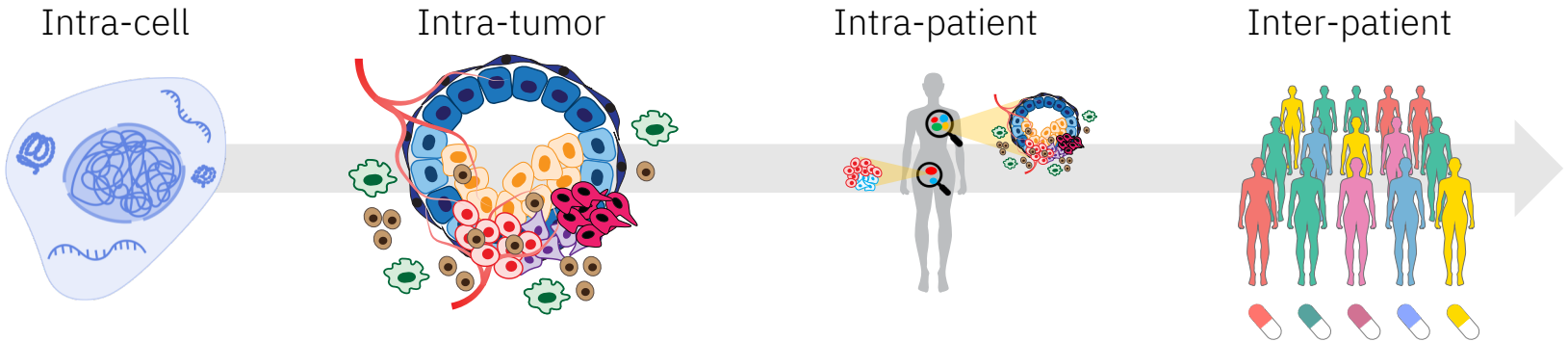


Image from: Hanahan et al., 2022

Spatial tumor heterogeneity across scales



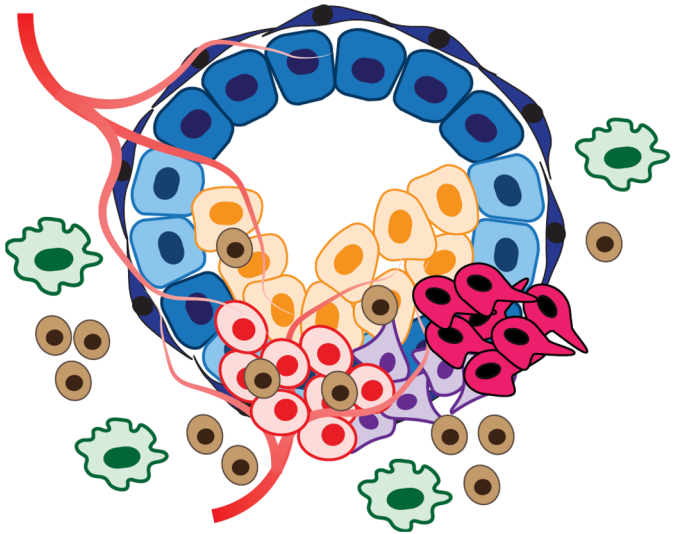
How do cancer subpopulations interact with each other and the TME?

How do they evade immune destruction and treatments?

How does the TME influence tumor growth?

Spatial heterogeneity as an **opportunity** to enable novel biomarker and therapeutic discovery

Spatial omics: the new frontier



Spatial transcriptomics:
e.g., smFISH, MERFISH, seqFISH, LCM, Visium, FISSEQ

Spatial proteomics:
e.g., mIHC, CycIF, CODEX, ImmunoSABER, IMC, MIBI

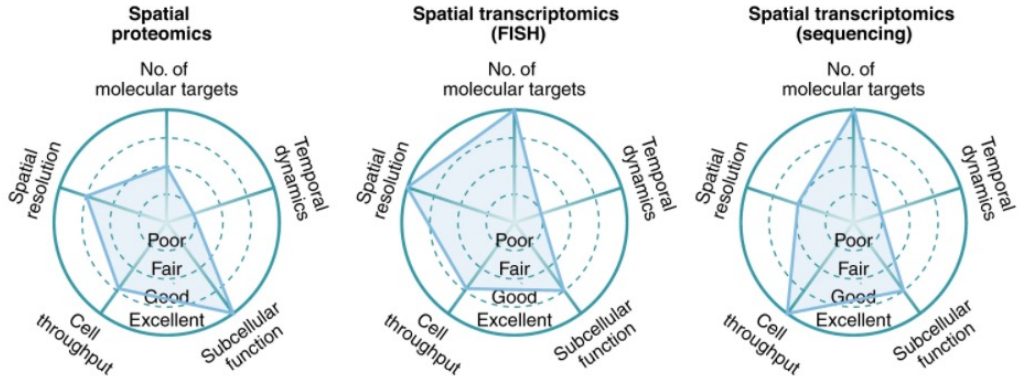


Figure from: Lewis *et al.*, *Nature Methods*, 2021

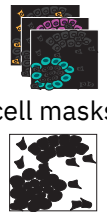
ATHENA

Analysis of Tumor Heterogeneity
from Spatial Omics Measurements

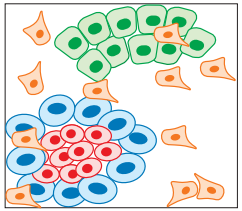
Spatial Omics Datasets

raw data

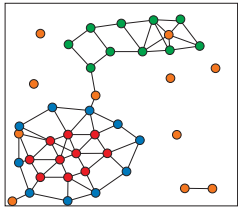
cell masks



cell phenotypes

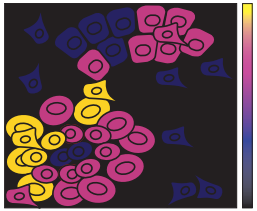


Graph Representation

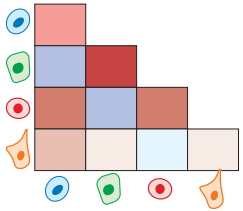


Spatial Heterogeneity Quantification

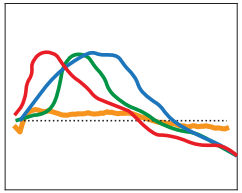
tumor diversity



cell interactions

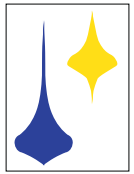


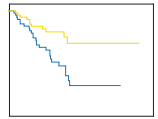
spatial patterns



Downstream Analysis

statistical / survival analysis

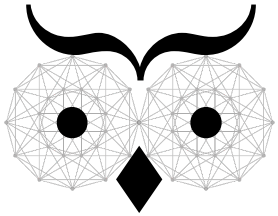




Implemented in Python

https://github.com/AI4SCR/ATHENA

Adriano Martinelli

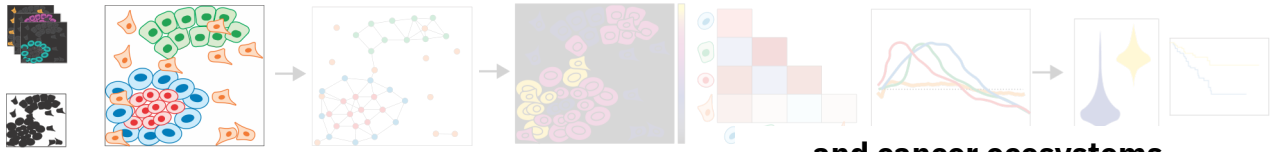


Spatial Omics Datasets

Graph Representation

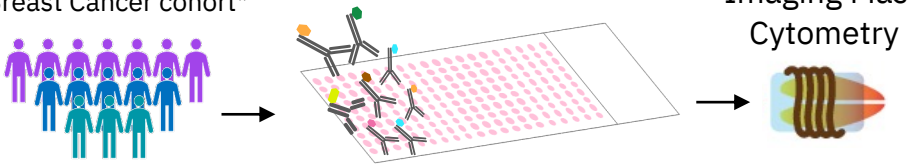
Spatial Heterogeneity Quantification

Downstream Analysis



From multiplexed imaging...

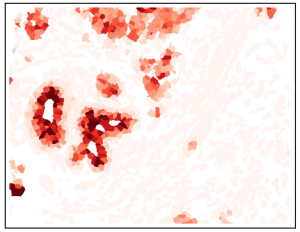
Breast Cancer cohort*



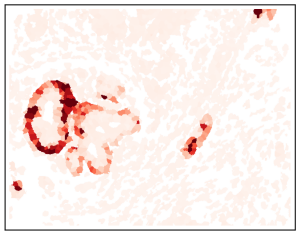
Imaging Mass Cytometry

... to single-cell spatial proteomics

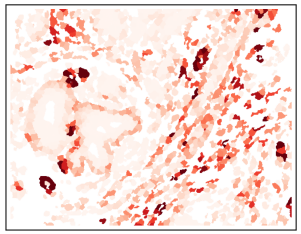
Pan Cytokeratin



Cytokeratin 5

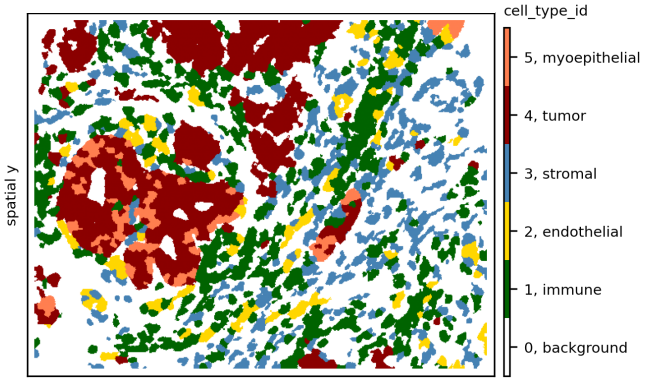


Smooth Muscle Actin

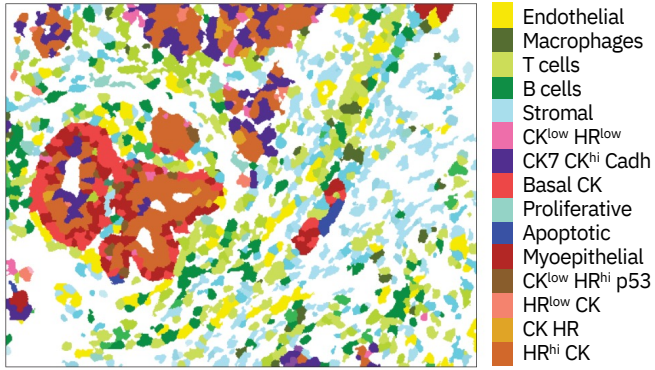


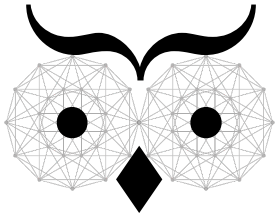
*Example data from Jackson *et al.*, *Nature*, 2019

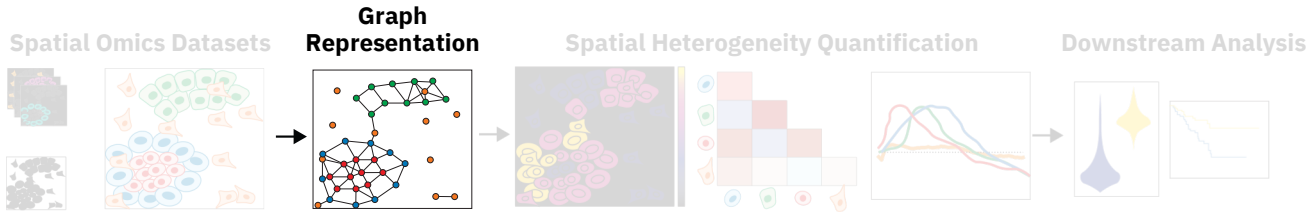
... and cancer ecosystems



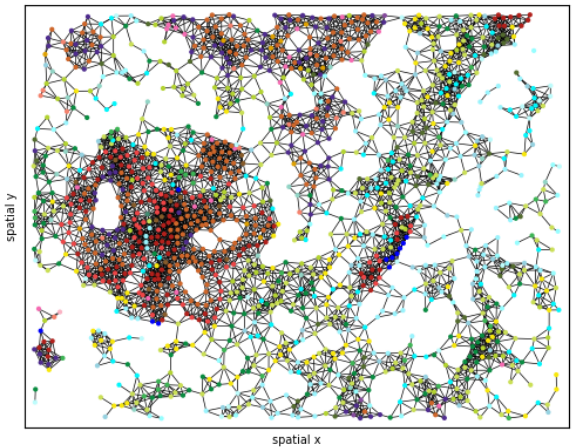
Annotated subpopulations



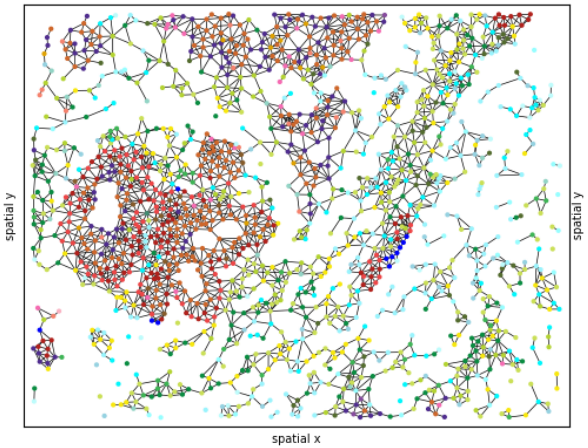




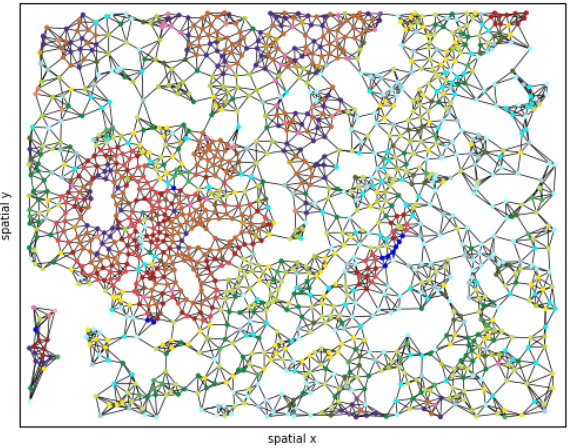
Radius Graph

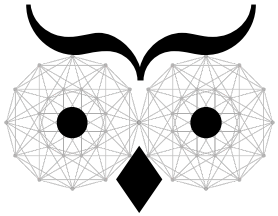


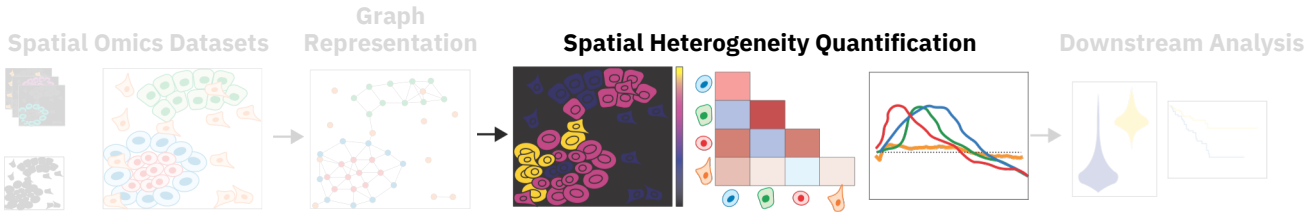
Contact Graph



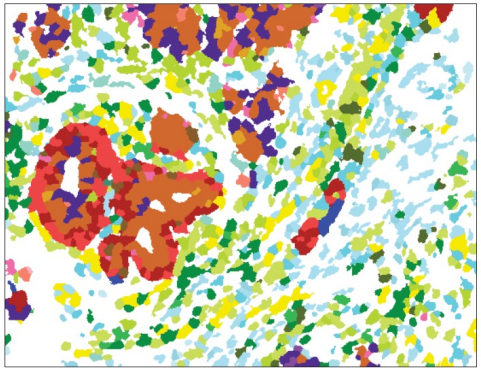
k-NN Graph







Spatially resolved phenotypes

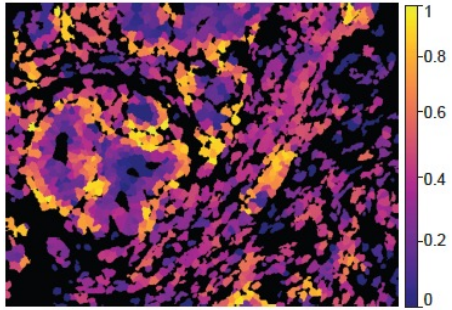


Endothelial
Macrophages
T cells
B cells
Stromal

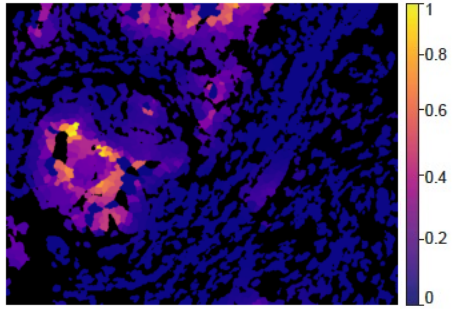
CK^{low} HR^{low}
$CK7^{+}$ CK^{hi}
Basal CK
Proliferative
Apoptotic

Myoepithelial
CK^{low} HR^{hi} $p53^{+}$
HR^{low} CK^{+}
HR^{+} CK^{+}
HR^{hi} CK^{+}

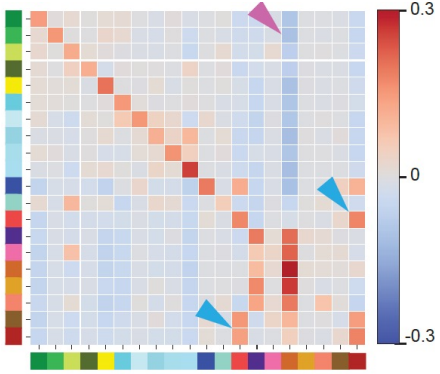
Local entropy



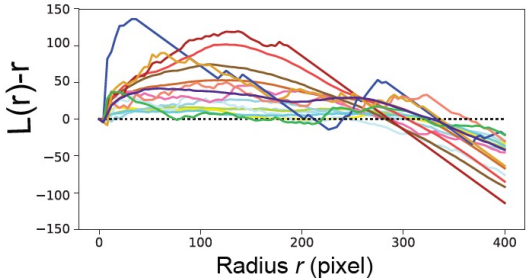
Immune infiltration



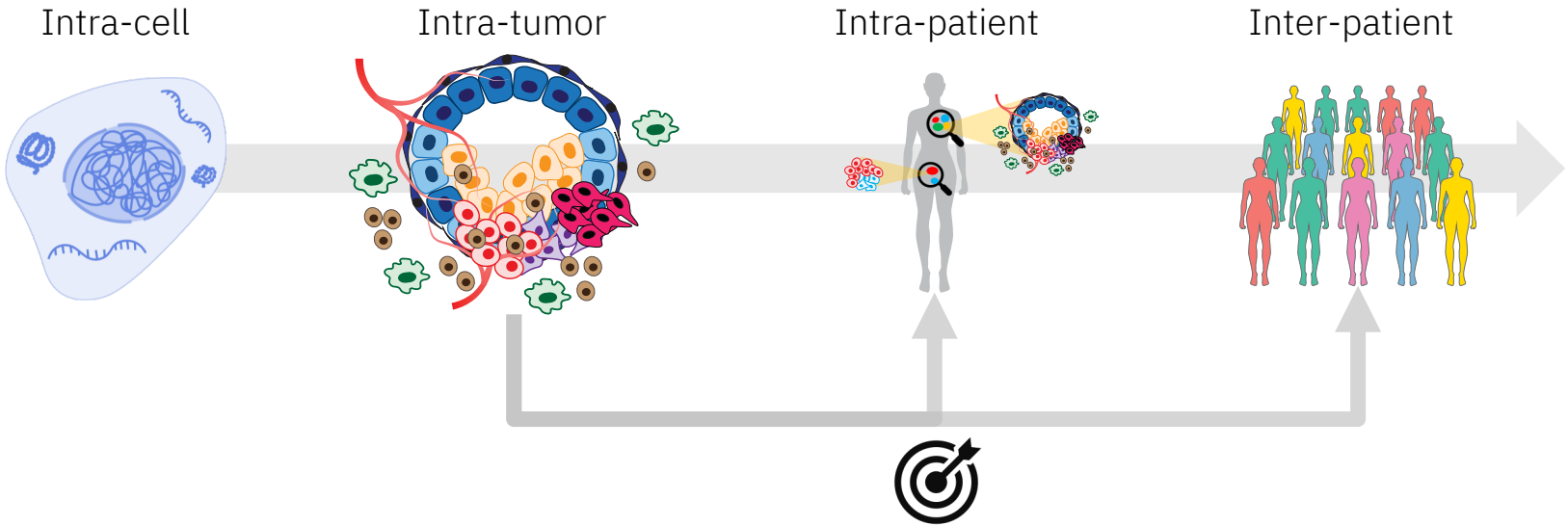
Cell interaction scores



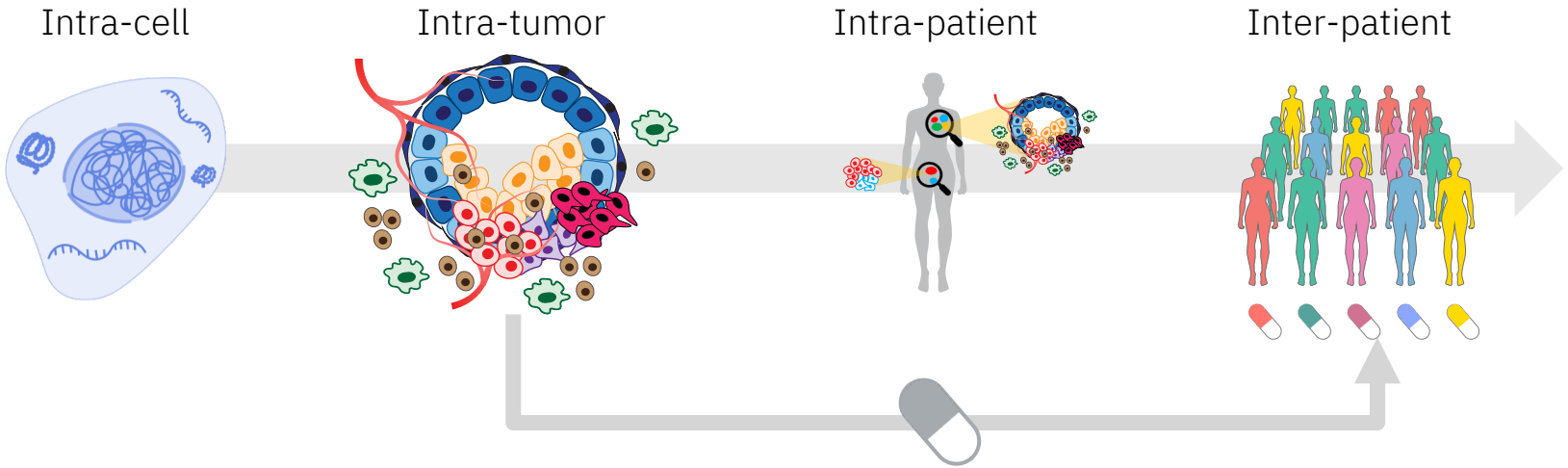
Cell clustering or dispersion



Towards heterogeneity-aware precision therapies



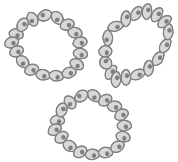
Towards heterogeneity-aware precision therapies



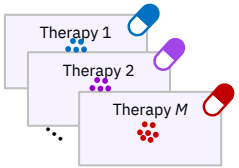
Spatial heterogeneity as an **opportunity** to enable novel biomarker and therapeutic discovery

PROMETEX | Metabolically-instructed personalized therapy selection for prostate cancer

Patient-Derived Organoids

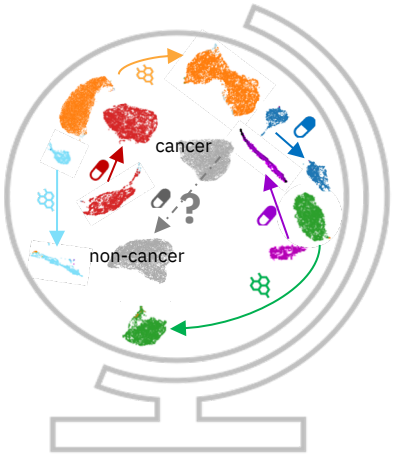


Single-Cell Metabolomics



Machine Learning Models

Atlas of Metabolic States



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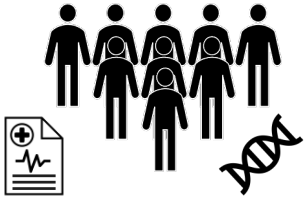
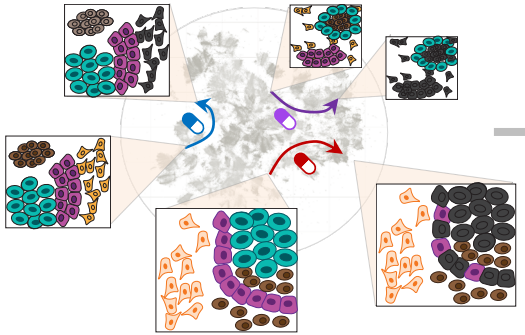
ARIES | AI-driven personalized therapy approach based on PCa ecosystem

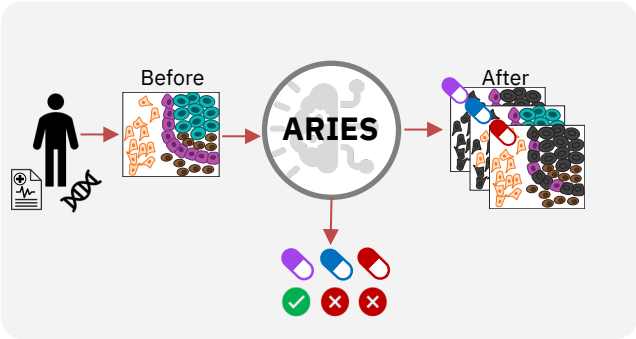
Prostate Cancer Cohort



Spatial Perturbation Atlas



Graph Representation Learning



In silico prediction of drug perturbations

Personalized drug response prediction

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Acknowledgements

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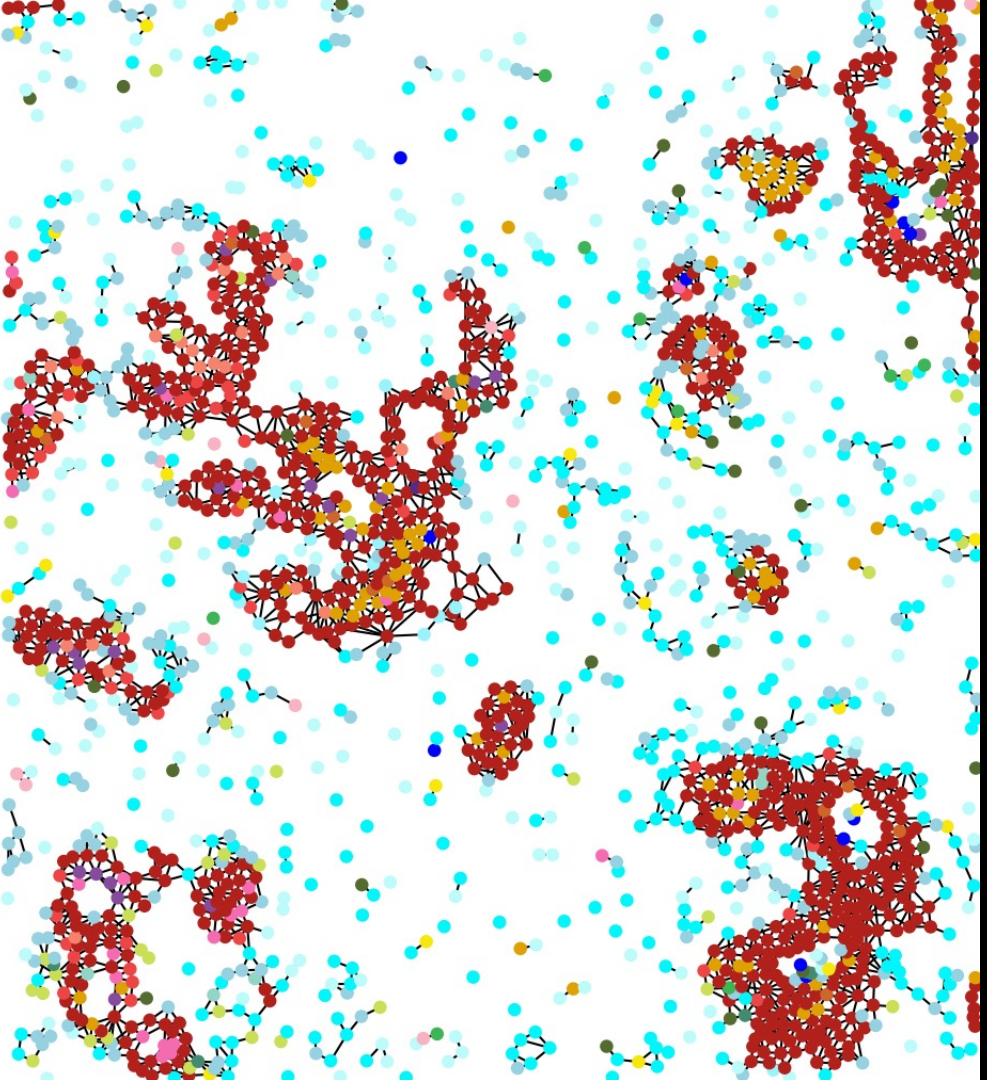
github.com/AI4SCR
github.com/histocartography

Swiss National Science Foundation



Thank you for the attention!

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